REMARKS

Reconsideration of this application in view of the above amendments and following remarks is respectfully requested. Prior to the present amendment, claims 1-38 were pending. Claims 18-31, 33, and 35 were previously withdrawn from prosecution. Claim 39 was previously cancelled.

By the present amendment, claims 2-14 and 18-38 are cancelled. New claims 40-43 are added, and claim 1 is amended to more specifically recite particular embodiments of the present invention. Support for these amendments may be found throughout the specification and claims as originally filed. Specific support for receptor proteins having the ability of being specifically bound by a ligand of the receptor protein is provided, *e.g.*, at page 5, lines 10-13. Support for biotinylated fusion proteins is provided throughout the instant specification, including, *e.g.*, at page 51, lines 12-16, and page 23, line 22 to page 24, line 3. Therefore, the amendments do not constitute new matter.

It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Upon entry of the present amendment, claims 1, 15-17, and 40-43 will be pending.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 2-14, 32, 34, and 36-38 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite. More specifically, the Examiner alleges that these claims recite a product made by a process and that the recited processes do not appear to provide product limitations that further limit the product of claim 1. Without acquiescence to this basis of rejection, these claims have been cancelled by the present amendment, thereby obviating this basis of rejection.

Claim 17 also stands rejected as indefinite. The Examiner asserts that it is unclear whether the recited adaptation for a specific detection method requires further product limitations.

Applicants traverse this basis of rejection and submit that the skilled artisan would readily appreciate that receptor chips adapted for various specific detection methods possess distinct characteristics as compared to the receptor chip of claim 1. As noted in the previous Amendment filed July 13, 2005, adaptation of the chip for detection by the techniques recited is clearly recognized by one skilled in this field as adding further limitation to the claim. For example, in the case of surface plasmon resonance detection, an appropriate dielectric and/or metal layer may be utilized to adapt the chip for such detection. Appropriate limitations are also associated with adaptation of the chip for detection by quartz-crystal microbalance and by mass spectroscopy, which additional features are clearly recognized and appreciated by one skilled in these different fields of detection. Furthermore, the term "adapted," in and of itself, indicates that the receptor chip of claim 17 is modified as compared to the receptor chip of claim 1.

Applicants also note that the Examiner has not provided further clarification regarding this basis of rejection and has not commented on the remarks addressing the same submitted in the Amendment filed July 13, 2005. For the reasons noted above, Applicants strongly disagree with the Examiner's view that a receptor chip "adapted for various specific detection methods" is not further limited as compared to the receptor chip of claim 1, which lacks any such requirement. According, Applicants submit that claim 17 satisfies the second paragraph requirements of §112 and request that this basis of rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 102

Claims 1-15, 32, and 36 stand rejected under 35 U.S.C. § 102(b) as anticipated by Holtzman *et al.* Specifically, the Examiner alleges that Holtzman *et al.* teaches a receptor chip comprising a recombinantly expressed receptor protein, TANGO 402, that is immobilized via a factor capable of specifically binding to biotin and is a member of an LDL receptor related protein family. The Examiner's rejection of claims 2-14, 32 and 36 appears based upon her belief that the processes recited in these claims do not appear to provide further product limitations as compared to claim 1. Without acquiescence to this basis of rejection, claims 2-14, 32, and 36 have been cancelled by the present amendment.

As applied to claims 1 and 15, Applicants submit that these claims are clearly not anticipated by Holtzman *et al.*, since this reference fails to teach a receptor chip possessing each characteristic recited in the instant claims. The instant claims are drawn to a receptor chip comprising a recombinantly expressed receptor protein that has been biotinylated *in vivo*. Holtmann *et al.* fails to teach a receptor chip comprising a biotinylated protein that has been biotinylated *in vivo*. Rather, Holtzmann *et al.* merely suggests that biotinylated polypeptides can be prepared using *in vitro* biotinylation methods. It is well known in the art that the biotinylated protein resulting from *in vivo* biotinylation is structurally different from the biotinylated protein resulting from *in vitro* biotinylation. Such structural differences are inherent to the biotinylation method used, and the skilled artisan fully recognizes and appreciates that the resulting bioltinylated proteins are structurally distinct.

In vitro biotinylation methods are performed by chemical means that involve the modification of protein amino groups with biotin-N-hydroxysuccinimide or a similar acylating agent. For example, Invitrogen Life Technologies markets *in vitro* biotinylation kits (ProtoArray™) that utilize a biotin-sulfosuccinimidyl ester, which reacts with the amine group of lysine residues within a protein to yield a biotin moiety covalently attached to the protein. The biotinylated protein resulting from *in vitro* biotinylation contains biotin moieties attached to various lysine residues throughout the protein.

In vivo biotinylation methods are performed enzymatically, typically by an endogenous biotin protein ligase present within the bacterial host used for recombinant expression of a biotinylated protein. Biotin ligases are enzymes of extraordinary specificity. For example, BirA, the biotin protein ligase of *E. coli*, biotinylates only a single cellular protein, the BCCP (AccB) subunit of acetyl-CoA carboxylase (Choi-Rhee, E. *et al.*, *Protein Science* 13:3043-3050, 2004). This specificity results from biotin ligases only targeting lysine residues present at particular locations within very specific amino acid sequences, which are not generally present in mammalian protein. Accordingly, *in vivo* biotinylation methods involve producing a recombinant protein of interest that is tagged with a biotin ligase target sequence by expressing the tagged protein in a host cell that contains the biotin ligase, so the protein is biotinylated *in*

vivo. The resulting *in vivo* biotinylated protein contains a single biotin moiety attached to a specific lysine residue within the biotin ligase target sequence fused to the protein of interest.

Given the clear and well-recognized structural differences between proteins biotinylated *in vivo* and proteins biotinylated *in vitro*, Applicants submit that Holtzman *et al.*'s reference to *in vitro* biotinylated proteins cannot anticipate the presently claimed invention, which is directed to structurally distinct *in vivo* biotinylated proteins. Thus, Applicants respectfully request that the Examiner withdraw this basis of rejection as applied to claims 1 and 15.

Rejections Under 35 U.S.C. § 103

Claims 16, 34, 37, and 38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Holtzman *et al.* as applied to claims 1 and 32, in view of Moriwaki *et al.* More specifically, the Examiner alleges that Holtzman *et al.* teaches a receptor chip comprising an immobilized receptor protein of the LDL receptor related protein family, but concedes that Holtzman *et al.* does not teach the receptor protein being LOX-1. Rather, the Examiner asserts that Moriwaki *et al.* remedies this deficiency by teaching that the receptor protein of LOX-1 binds to a protein moiety of Ox-LDL and may be used to define ligand specificities of LOX-1. The Examiner concludes that it would have been obvious to immobilize LOX-1 on the receptor chip of Holtzman *et al.*, in order to provide a more efficient testing surface for performing automated binding assays and facilitating the separation of complexed and uncomplexed forms of LOX-1. The Examiner indicates that the processes recited in claims 3, 4, 7, and 38 do not provide further product limitations as compared to claims 1 and 32.

Claim 17 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Holtzman *et al.*, as applied to claim 1, in view of Duffy *et al.* The Examiner alleges that Holtzman et al. teaches a receptor chip comprising an immobilized receptor protein adapted for ELISA detection, but concedes that Holtzman *et al.* does not teach a receptor chip adapted for detection by mass spectrometry. The Examiner asserts that Duffy *et al.* teaches adapting a surface for use with ELISA or SPR. The Examiner asserts that it is well known in the art that ELISA detection is functionally equivalent to SPR detection, so it would have been obvious to

substitute SPR detection, as taught by Duffy *et al.* for ELISA detection, as taught by Holtzman *et al.* In addition, the Examiner contends that such a substitution would be motivated based upon economics and availability of detection equipment.

Applicants note that claims 34, 37, and 38 have been cancelled without acquiescence to these rejections. Thus, the following comments are directed to the patentability of claims 16 and 17.

Applicants respectfully traverse these bases of rejection and submit that the Examiner has failed to establish a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)). In the instant case, the Examiner has failed to meet this requirement.

Neither of the cited combinations of references teach each element of the claimed invention and, therefore, they cannot render obvious the claimed receptor chip comprising a recombinantly expressed receptor protein that has been biotinylated *in vivo*. Specifically, as described above, Holtzman *et al.* fails to teach a receptor chip comprising a receptor protein that is biotinylated *in vivo*, as recited in claim 1 and, thus, claims 16 and 17, dependent therefrom. Neither Moriwaki *et al.* nor Duffy *et al.* remedy this deficiency in the Examiner's *prima facie* case, since neither of these references describe a receptor protein that is biotinylated *in vivo*. Accordingly, these combinations of references clearly fail to render the claimed receptor chip obvious.

In addition, even assuming *arguendo* that one of the cited references taught advantages associated with *in vivo* biotinylation, a person having ordinary skill in the art would

have no reasonable expectation of achieving the presently claimed invention with any reasonable expectation of success. In particular, absent the present application, a person having ordinary skill in the art would not reasonably have expected to recombinantly produce a biotinylated receptor protein that is capable of binding a ligand of the receptor protein, as presently claimed, particularly in quantities sufficient to prepare a receptor chip. As described in the instant application and understood in the art, receptor proteins are membrane proteins and, therefore, do not lend themselves to recombinant production in a soluble form capable of binding to a ligand. Rather, the hydrophilic properties of receptor proteins cause them to accumulate as inactive aggregates, *i.e.*, inclusion bodies, during recombinant production (*see*, page 3, lines 8-26).

It is only the present invention that provides, in particular embodiments, a method of recombinantly expressing a biotinylated receptor protein capable of binding to a ligand when immobilized on a receptor chip. As described throughout the instant application, these methods include biotinylating the receptor protein *in vivo*, such that the attached biotin moiety does not interfere with ligand binding and such that the receptor protein can be attached to a chip in a manner that permits ligand binding. In addition, these methods include refolding the inactive receptor protein inclusion bodies in a solution containing a cyclic carbohydrate and a polyoxyethylene detergent or a solution containing a cyclic carbohydrate and an ionic detergent, such that the receptor protein is refolded in an active conformation that binds to a ligand. Accordingly, the skilled artisan would have no reasonable expectation of successfully producing the presently claimed receptor chip comprising a receptor protein that was biotinylated *in vivo* and is capable of binding a ligand of the receptor protein, absent the teachings of the instant application.

Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection, as applied to claims 16 and 17, in light of the above amendments and remarks.

New Claims

Lastly, Applicants have added new claims 40-43, which are specifically directed to an embodiment of the present invention wherein the receptor matrix comprises a recombinant biotinylated fusion protein comprising a receptor protein and a polypeptide comprising a

biotinylation sequence motif, wherein the biotinylation of the fusion protein has been carried out within a bacterial host. Applicants submit that support for these claims may be found throughout the instant specification, including, *e.g.*, at page 51, lines 12-16, and page 23, line 22 to page 24, line 3, and their introduction does not constitute new matter.

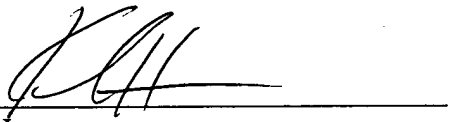
Applicants submit that new claims 40-43 are patentable over the cited references for the same reasons discussed above.

Conclusion

In view of the above amendments and remarks, allowance of claims 1, 15-17 and 40-43 is respectfully requested. A good faith effort has been made to place this application in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at (206) 622-4900 to resolve the same.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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